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Celiac Disease and Immunoglobulin A Deficiency: How Effective Are the Serological Methods of Diagnosis?

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Immunoglobulin A (IgA) deficiency is 10 to 15 times more common in patients with celiac disease (CD) than in healthy subjects. Serological tests have become the preferred methods of diagnosing CD in both symptomatic and asymptomatic patients. However, commercially available serological methods are limited in that they detect only the IgA isotype of antibodies (with the exception of IgG gliadin assays); hence, IgA-deficient patients with CD may yield false-negative serology. Fifteen pediatric patients with CD and 10 IgA-deficient pediatric patients without CD were examined for IgA and IgG antibodies to endomysium, gliadin, and tissue transglutaminase. Twenty-five specimens from patients with IgA deficiency were examined. Fifteen were from patients with CD, and 10 were patients without CD. All 15 IgA-deficient patients with CD were positive for endomysium antibodies of the IgG isotype and for IgG gliadin antibodies. All but one of the IgA-deficient patients with CD were also positive for IgG tissue transglutaminase antibodies. None of the IgA-deficient patients without CD were positive for any of the antibody markers. All the specimens examined were also negative for IgA-specific antibodies to endomysium, gliadin, and tissue transglutaminase. IgG-specific antibody tests for endomysium, gliadin, and tissue transglutaminase are useful for the identification of IgA-deficient patients with CD. IgG antibody tests along with tests routinely being used in clinical laboratories can reliably detect all active patients with CD. In addition, the levels of these CD-specific IgG antibodies could be used to monitor patient dietary compliance.

Celiac disease (CD) is a permanent intolerance to gluten characterized by villous atrophy and signs of immunological activation in the lamina propria of the jejunum. Not all patients with CD manifest classical histopathology of CD; hence, a significant number of patients with gluten-sensitive enteropathy may not be recognized by the histological criteria (1, 7, 16, 17, 22). Delays in the diagnosis of CD may increase a patient's susceptibility to other autoimmune diseases, such as diabetes, and/or to complications of gluten-sensitive enteropathy, such as intestinal lymphoma (5, 6, 9, 11, 19, 20).

Recently, serological methods of detecting antibodies to gliadin (AGA), endomysium (EMA), reticulin (ARA), and tissue transglutaminase (tTG antibody) have become the preferred methods of diagnosing both symptomatic and asymptomatic patients with CD. These antibody tests either individually or in combination can reliably diagnose almost all cases of CD when patients are on a gluten-containing diet. In addition, as the levels of these antibodies decline with the absence of gluten from the diet, they can be used to monitor a patient's response to a gluten-free diet (GFD). Serum antibody tests, therefore, have twofold significance: (i) they reliably identify patients with gluten-sensitive enteropathy, and (ii) they monitor the effectiveness of and adherence to a GFD.

The limitations of the current serological methods, however, is that, with the exception of IgG-type gliadin, they detect the IgA isotype of the antibodies; hence, specimens from IgA-deficient patients with CD may yield false-negative serology (21). Due to the sensitivity and specificity of the EMA and tTG antibody methods, the AGA methods are not necessarily employed in every laboratory. This may compromise the utility of the serum antibody methods in detecting all patients with CD (12, 13). IgA deficiency is one of the most frequent immunodeficiencies, found in one in 500 to 700 healthy blood donors (23; D. Lilic and W. A. Sewell, Letter, J. Clin. Pathol. **54:**337-338, 2001). In most situations, these IgA-deficient individuals are healthy, and those who develop symptoms suffer from sinopulmonary infections, allergies, and autoimmune disorders, especially CD (24). The incidence of IgA deficiency in patients with CD is somewhere between 2 and 3%, representing an increase of 10- to 15-fold over the general population. To prevent false-negative results in such cases, it is necessary to have simple, reliable serological methods of detecting IgG type of antibodies.

In the study, we examined the utility of the IgG-based immunoassays for EMA, tTG antibody, and AGA in diagnosing IgA-deficient patients with CD. We studied 15 IgA-deficient patients with CD and 10 IgA-deficient patients without CD for IgG and IgA EMA, tTG antibody, and AGA. These studies suggest the importance of IgG EMA, AGA, and tTG antibody for diagnosing IgA-deficient patients with CD.

MATERIALS AND METHODS

Antibody detection methods. (i) Specimens. Serum specimens were collected from 15 patients suspected of CD but with IgA deficiency. Similarly, for controls, serum specimens were obtained from 10 IgA-deficient patients without CD.

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TABLE 1. Clinical profile of IgA-deficient patients with CD included in the study

Patient no.	Age (yr) at onset of symptoms	Age (yr) at which IgA deficiency established	Age (yr) at which jejunal biopsy performed (grade of villous atrophy)	Frequency of infection or related conditions	Therapy	Family history
1	12	12	12	None	None	Brother, food allergy; mother, Sjogren syndrome
2	2	4	ND[a]	None	None	Grandmother's brother died of enteritis
3	<1	3	3 (IV)	None	None	None
4	<1	4	ND	None	None	None
5	<1	1	1 (IV)	Few/year	None	None
6	<1	10	1 (IV)	Few/year	None	None
7	16	16	16 (IV)	Recurrent diarrhea in early years	None	None
8	6	10	ND	Inflammatory skin disease	None	None
9	2	2	2 (IV)	Yes	None	None
10	2	ND	2 (IV)	Allergies	Inhalation steroids, antiallergy medications	None
11	14	16	14 (IV)	None	None	None
12	1	1	1 (IV)	None	GFD	Gut disorder on mother's side
13	6	7	ND	ND	ND	ND
14	2	11	2 (IV)	None	ND	ND
15	1	14	14 (III)	Yes	None	None

[a] ND, not done.

Most of these specimens were drawn from children. In 10 of 15 children with IgA deficiency, onset of first clinical symptoms of CD occurred at 2 years of age or younger; in two of these cases, the serum antibody measurements were also made at the age of 2 years or younger (Table 1). A majority (if not all) of the control subjects included in the study were patients in whom CD has been suspected based upon their clinical presentation of diarrhea, small body mass, and enteritis (Table 2).

(ii) Immunofluorescence. The presence of EMA was determined by indirect immunofluorescence on 4-μm-thick cryostat sections of primate distal esophagus or the primate (monkey) smooth muscle as the antigenic substrate (IMMCO Diagnostics, Inc., Buffalo, N.Y.). Sections of the primate tissue were incubated at room temperature for 30 min with patient sera at a 1:2.5 dilution. After washing the unreacted serum proteins with phosphate-buffered saline, the bound antibodies were detected by incubating the substrate with fluorescein-labeled anti-human IgA or IgG conjugates for 30 min. The presence of EMA reactions was detected by reading under the Eclipse E600 fluorescence microscope (Nikon, Inc., Melville, N.Y.).

(iii) ELISA. AGA and tTG antibody of IgG and IgA isotypes were measured by enzyme-linked immunosorbent assay (ELISA) with kits manufactured by IMMCO Diagnostics, Inc.. Patient sera were tested at a 1:51 dilution. The presence of antibodies bound to the antigen-coated microwells was detected by incubating with alkaline phosphatase-labeled anti-human IgG or IgA conjugates followed by the addition of paranitrophenyl phosphate substrate. After stopping the reaction with the stopping buffer, readings were made at 405 nm. Results were expressed in arbitrary ELISA units as determined from 3 standard deviations of the mean of the results obtained for healthy donors. The ELISA unit values of the patient samples were derived from the standard curve obtained from a set of calibrators provided in the kit. Values greater than 20 EU/ml were considered to be positive.

TABLE 2. Clinical profile of IgA-deficient control subjects included in the study[a]

Patient no.	Age (yr)	Clinical symptom(s)	Duration (mo.) of GFD	Duration (mo.) of gluten challenge
1	2	Small body mass	None	None
2	3	Small body mass, enteritis	24	6 (no effect)
3	2	Small body mass, diarrhea	12–14	8 (no effect)
4	2	Small body mass, diarrhea	None	None
5	3	Small body mass	None	None
6	5	Anemia, diarrhea	None	None
7	7	Small body mass, food allergy	7	Yes (no effect)
8	3	Diarrhea	12	Yes (no effect)
9	1	Small body mass, growth retardation, cerebral palsy	None	None
10	1	Diarrhea, small body mass	None	None

[a] Jejunal biopsy was performed on patients 2 and 6. Only in patient 2 was there villous atrophy (grade II/III). At the time of study, all subjects were on a Normal (gluten containing) diet.

RESULTS

Patients with CD (n = 15) and without CD (n = 10) with selective IgA deficiency examined over a period of time were selected for studying the efficacy of various serological methods for diagnosing CD. In 9 of the 15 IgA-deficient patients with CD, the onset of clinical symptoms started before the age of 2 years, and in 10 of the 15 cases the IgA deficiency was established soon after the patient exhibited clinical manifestations. Eleven of these 15 patients underwent endoscopic examination of the jejunum. All eleven patients examined had villous atrophy and morphological changes consistent with CD. One of the patients was on a GFD for a prolonged period of time at the time of examination for autoantibodies associated with CD (Table 1).

EMA, AGA, and tTG antibodies of both IgA and IgG isotype were measured using well-standardized methods. EMA were detected on primate smooth muscle rather than the distal esophagus as it provided a large antigenic substrate area for examination.

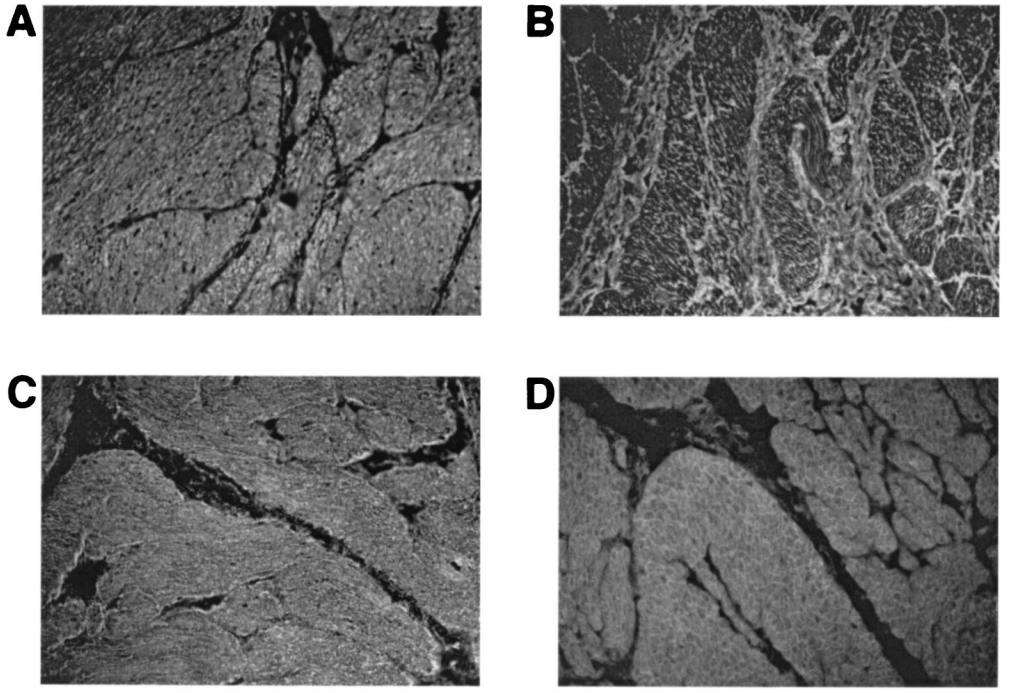

FIG. 1. Indirect immunofluorescence reactions on primate smooth muscle tissue for EMA detection depicting the following: (A) prozone reactions at low dilution (weak EMA reactions), (B) same serum at higher dilution (strong EMA reactions); (C) concomitant presence of smooth muscle and EMA (pepper like reaction); (D) non-EMA reaction.

Precautions were followed to discriminate EMA IgG-positive reactions from other antibody reactions. The antibodies were detected at a starting dilution of 1:2.5 and at 1:20 to detect potential prozone effects. Nearly all of the IgA-deficient patients with CD examined had high titers of IgG-EMA and some of these specimens exhibited prozone effect (Fig. 1A and B). Testing at both 1:2.5 and 1:20 also prevented any false-negative results due to the presence of coexisting autoantibodies binding to the substrate. The most common interfering antibody is anti-smooth muscle antibodies and obscuring the presence of EMA. Concomitant presence of EMA and smooth muscle antibodies provide a pepper-like reaction (Fig. 1C). The smooth muscle antibody titer is usually lower than that of EMA, and hence at higher dilutions the EMA reactions become more easily recognizable. Occasionally one may observe reactions that could be confused for EMA and need to be taken into consideration in the readings (Fig. 1D). Using the criteria mentioned above, EMA IgG antibodies were found in all IgA-deficient patients with CD on a normal gluten-containing diet. It is noteworthy that all patients had very high titers of EMA IgG antibodies, and none of them were positive for EMA IgA antibodies. Similarly, specimens from all IgA-deficient patients with CD were also positive for high concentrations of AGA IgG antibodies, and all but one was positive for tTG antibodies (Table 3). One IgA-deficient patient with CD on a GFD for an extended period of time was completely negative for antibodies to all three antigens, suggesting that antibody levels are associated with gluten intake. None of the IgA-deficient patients without CD were positive for IgG- or IgA-type EMA, AGA, or tTG antibody.

TABLE 3. Immunological findings in patients with IgA deficiency

Patient group and no.	Titer of EMA		Level of antibody[a] (ELISA units/ml)			
			AGA		tTG	
	IgA	IgG	IgA	IgG	IgA	IgG
With CD						
1	NEG[b]	2,560	NEG	95	NEG	88
2	NEG	1,280	NEG	56	NEG	75
3	NEG	5,120	NEG	>160	NEG	>117
4	NEG	1,280	NEG	>160	NEG	>117
5	NEG	2,560	NEG	>122	NEG	>117
6	NEG	640	NEG	75	NEG	98
7	NEG	2,560	NEG	>160	NEG	109
8	NEG	320	NEG	>160	NEG	86
9	NEG	1,280	NEG	>160	NEG	>117
10	NEG	1,280	NEG	122	NEG	>117
11	NEG	2,560	NEG	>154	NEG	>148
12[c]	NEG	<2.5	NEG	NEG	NEG	NEG
13	NEG	5,120	NEG	147	NEG	NEG
14	NEG	1,280	NEG	70	NEG	139
15	NEG	320	NEG	135	NEG	121
Without CD						
1	NEG	NEG	NEG	NEG	NEG	NEG
2	NEG	NEG	NEG	NEG	NEG	NEG
3	NEG	NEG	NEG	NEG	NEG	NEG
4	NEG	NEG	NEG	NEG	NEG	NEG
5	NEG	NEG	NEG	NEG	NEG	NEG
6	NEG	NEG	NEG	NEG	NEG	NEG
7	NEG	NEG	NEG	NEG	NEG	NEG
8	NEG	NEG	NEG	NEG	NEG	NEG
9	NEG	NEG	NEG	NEG	NEG	NEG
10	NEG	NEG	NEG	NEG	NEG	NEG

[a] ELISA values of >20 were considered positive for both AGA and tTG antibody.
[b] NEG, negative.
[c] IgA-deficient patient on GFD for prolonged period of time.

DISCUSSION

Selective IgA deficiency, as defined by the total or severe deficiency of the IgA immunoglobulins in serum and secretions, is the most common of the immunodeficiency disorders (Lilic and Sewell, letter). Studies suggest that 1 in every 500 people may have selective IgA deficiency. Even though a large number of individuals with selective IgA deficiency are relatively healthy, there are many affected with various illnesses. These include recurrent infections, allergies, and autoimmune disorders (23, 24). The prevalence of IgA deficiency in patients with CD is 10 to 15 times higher than that in the general population (2, 3, 8, 15, 18; H. R. Gillett, P. M. Gillett, K. Kingstone, T. Marshall, and A. Ferguson, Letter, J. Pediatr. Gastroenterol. Nutr. **25:**366-367, 1997). For this reason it is suggested that patients with IgA deficiency should be considered as an at-risk group for CD. Cataldo et al. (2, 3, 4) have reported that the clinical presentation of patients with CD with selective IgA deficiency is different from that of patients with CD with normal IgA levels, demonstrating a greater incidence of the silent form. Because of the mild form of clinical presentation in IgA-deficient patients with CD, there may be an extended delay in recognizing such cases before an appropriate GFD therapy can be instituted.

Due to the varied clinical presentations and the fact that two-thirds of patients with CD have either the asymptomatic or silent form of CD, there has been much more emphasis on the serological methods for detecting all forms of CD. The serum antibody markers that are being used are AGA, ARA, EMA, and tTG antibody. These serological markers are highly sensitive and specific markers for CD, especially for IgA-based antibody tests. Of the various markers, EMA has proven to be the most specific and sensitive marker, with positive and negative predictive values approaching 100% (12, 13, 26). Because of the high prevalence of IgA deficiency in patients with CD, attention has been focused on the problem of IgA-deficient patients with CD and the methods of diagnosing them. IgA deficiency can lead to false-negative serology, as most of the existing serological methods detect only IgA antibodies (21). The only serological test that can detect IgG antibodies related to CD is the AGA test. However, as the AGA IgG antibody test has limited specificity (76 to 80%), this test alone may not reliably establish a definitive diagnosis. Some investigators have suggested that IgA levels be measured in all specimens submitted for CD and a biopsy be performed in on IgA-deficient patients. However, there is a concern that routine IgA testing of all suspected cases of CD may lead to unnecessary biopsy (14).

In 1989, Beutner et al. (E. H. Beutner, V. Kumar, T. P. Chorzelski, and M. Szaflarska-Czerwionka, Letter, Lancet **i:**1261-1262, 1989) reported the first case of an IgA-deficient CD patient found negative for EMA IgA antibodies but positive for EMA, ARA, and AGA IgG antibodies. The levels of these antibodies disappeared when the patient was on a GFD and reappeared upon gluten challenge. This study suggested that IgG EMA antibody levels could be used to monitor IgA-deficient patients with CD for their compliance to GFD. Since this report, at least 36 similar cases of IgA-deficient patients with CD have been reported (Table 4). All tested positive for EMA IgG antibody, indicating the importance of EMA IgG antibody for diagnosing IgA-deficient patients with CD (2, 3, 4, 10, 21). The results for AGA IgG and tTG antibodies were less reliable than those for EMA IgG antibodies, as a few cases were missed by the tTG antibody and AGA IgG tests that were convincingly positive for the EMA IgG antibodies. The specificity of the EMA test in all studies was 100% in comparison with AGA and tTG antibody assays, as a few false positives were reported with these assays in the hands of some investigators. This agrees with the findings of Lagerqvist et al. (13) and others (10, 12, 26), who found the EMA test to provide the highest reliability in its sensitivity and specificity, compared with AGA or tTG antibody tests. This could be due to various factors, including the quality and source of the antigen as well as method standardization. Most of the ELISAs utilize a cutoff of positivity that is 2 or 3 standard deviations of the mean of the value for specimens from healthy subjects, thus providing a confidence interval of 95% in the majority of cases. In comparison, EMA tests performed according to good laboratory practices can approach 100% specificity and sensitivity. In our laboratory, we were able to achieve much better correlation between the AGA and tTG antibody results with EMA, as all 14 IgA-deficient patients with CD on normal diets were positive for AGA IgG antibody, and all but one were also positive for tTG antibodies. For the subject for whom a negative tTG antibody result was obtained the assay was repeated and the result was still found to be negative, suggesting that there may be other antigens involved in CD or that certain epitopes on tTG are masked for reacting to the antibodies. Our group and others have observed a similar phenomenon with IgA-normal patients with CD (10, 12, 25, 26). Cataldo et al. (4) reported all of their 24 patients to be positive for tTG antibodies; however, they also found 2 of the 10 IgA-deficient patients without CD

TABLE 4. Immunological antibody profile of patients with IgA deficiency

Study group and reference	No. of subjects	No. of subjects positive for:					
		EMA		AGA		tTG antibody	
		IgA	IgG	IgA	IgG	IgA	IgG
Patients with CD							
Cataldo et al. (4)	20	0	20	0	20	0	20
Korponay-Szabo et al. (10)	2	0	2	0	1	ND[a]	ND
Cataldo et al. (2)	54	0	ND	0	51	ND	ND
Cataldo et al. (3)	12	0	ND	0	12	ND	ND
Rittmeyer and Rhoads (21)	2	0	ND	0	1	ND	ND
Beutner et al.[b]	1	0	1	0	1	ND	ND
Present study	14	0	14	0	14	0	13
Patients with CD on GFD							
Cataldo et al. (4)	34	0	0	0	0	0	4
Cataldo et al. (2)	52	ND	0	ND	5	ND	ND
Beutner et al.[b]	1	0	0	0	0	ND	ND
Present study	1	0	0	0	0	0	0
Patients without CD							
Cataldo et al. (4)	10	0	0	0	0	0	2
Cataldo et al. (3)	2	0	ND	0	0	ND	ND
Present study	10	0	0	0	0	0	0

[a] ND, not done.
[b] Letter.

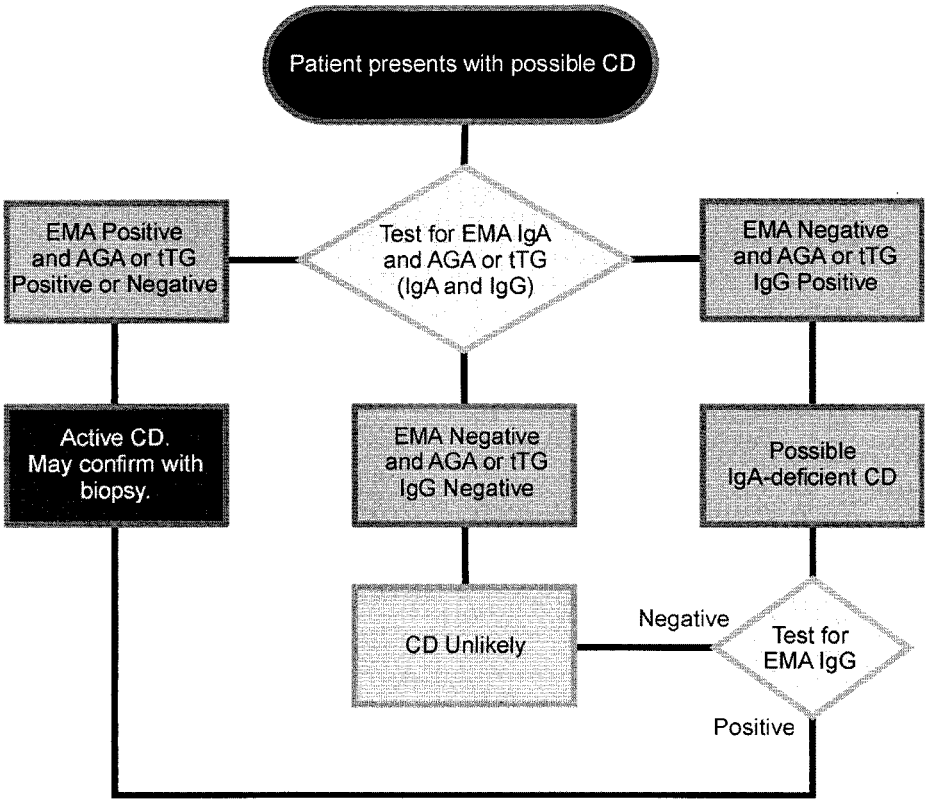

FIG. 2. Algorithm for serological screening of CD.

to be positive for tTG antibodies, raising questions about the specificity of their tTG antibody assay.

When patients are on a GFD, the antibody levels tend to decrease and eventually disappear. This is borne out by data for certain patients in our studies. In each study there was one patient with CD on GFD. In both cases the EMA and AGA IgG antibody levels were normal. The patient whose case is presented in this paper was also negative for tTG antibodies. This suggests that the level of these antibodies may be used to monitor the response of the patients to GFD, as is the case with IgA-normal patients with CD.

In conclusion, the data suggest that patients with CD with IgA deficiency have the IgG isotype of antibodies to the same antigens (EMA, AGA, and tTG antibody) as IgA-normal patients with CD. The use of these assays will enhance the reliability of the serological methods of detecting symptomatic, asymptomatic, and silent forms of CD, whether they are IgA normal or deficient. We provide an algorithm for serological investigation of patients suspected for CD (Fig. 2).

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